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Original Research Article

Effect of serum progesterone on the day of trigger administration to MII oocyte ratio on IVF/ICSI outcomes

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ABSTRACT

Background: To evaluate the effect of serum progesterone on the day of trigger administration to MII oocyte ratio on IVF/ICSI outcomes. Retrospective observational study in Institute of Reproductive Medicine, The Madras Medical Mission, Chennai.
Methods: 211 patients meeting inclusion and exclusion criteria were subjected to controlled ovarian stimulation with antagonist protocol and were serially monitored by ultrasound and hormonal blood tests and when at least 3 follicles reach 18 mm size, ovulation is triggered with HCG or GnRH agonist. Serum progesterone levels on the day of trigger were noted and oocyte retrieval done 35 hours after trigger injection and the no. of MII oocytes retrieved were noted. Embryo transfer was done on day 3 of oocyte retrieval. Adequate luteal support was given, Pregnancy test was done 16 days after embryo transfer.
Results: On evaluating 211 fresh ICSI–ET cycles, Roc curve was obtained and it showed that when compared with patients with P-trigger/MII oocyte ratio≤0.29 group, patients with P-trigger/MII>0.29 group had a lower clinical pregnancy rate, implantation rate and live birth rate.
Conclusions: The present study reveals that an elevated of P-trigger/MII oocyte ratio is inversely correlated with the probability of pregnancy, indicating that this ratio may be a reliable predictor of IVF outcomes. P/MII ratio could also play a key role in selection of patients for cryopreservation of all embryos (elective freeze-all policy) and subsequent transfer of cryopreserved/thawed embryos.

Keywords: IVF/ICSI outcomes, MII oocyte, P-Trigger /MII oocyte ratio, Serum progesterone on trigger day

INTRODUCTION

The impact of elevated serum progesterone (P) levels on the day of trigger administration in invitro fertilization (IVF) outcomes remains controversial, with numerous studies suggesting a negative effect on pregnancy success, while some studies have found no such association.[1-6] Current controlled ovarian stimulation (COS) protocols in assisted reproduction treatment (ART) cycles use either Gonadotropin-releasing hormone agonists (GnRHa) or antagonists to prevent premature luteinization before oocyte retrieval. Despite that however, subtle increase in progesterone prior to ovulation trigger occur in 5-35% of cycles.[5-9] The cause of this premature elevation of progesterone (PE) is still largely unknown. Whilst earlier reports claimed it to be related to premature elevation of LH, later reports however have shown it to be related to increased granulosa cells LH receptor and Progesterone (P) production even in the presence of low LH levels.[3,10-15] PE may disrupt endometrial glandular and stromal function, potentially advancing the implantation window, which could negatively affect embryo transfer outcomes.[16,17] Another postulated mechanism for negative

effect of PE is impaired oocyte/embryo quality.[18] The relationship between progesterone levels and endometrial receptivity remains complex, with variability in study findings. Relying on progesterone level which is a surrogate marker of endometrial receptivity may not be sufficient in predicting the result of IVF/ICSI cycles. Shuffaro et al proposed that elevated P may be only harmful if it represents an increased production of P per follicle.[19]

As P level elevation may correlate with the number of hormonally active oocytes, the P/oocyte ratio reflects the average amount of P produced by each oocyte on the day of final oocyte maturation.[19,20] Adjusting the ovarian response using the number of available mature oocytes (as a surrogate marker for available embryos) and P levels on the trigger day can be more reliable to reflect endometrial receptivity.

We have therefore proposed that the ratio of progesterone level to the number of mature metaphase II oocytes (P/MII) may serve as a more reliable predictor for implantation potential and clinical pregnancy rates, compared to traditional markers like progesterone levels alone. If validated, the P/MII ratio could offer clinicians a more pronounced approach to assess and manage ART cycles, potentially improving the patient outcomes.

METHODS

Study type

This is a retrospective observational study.

Study place

The study was conducted at the Institute of Reproductive Medicine, The Madras Medical Mission Hospital following approval from the institutional scientific and ethical committee

Study duration

The study was done during the period of January 2014 to January 2017.

Inclusion criteria

Female patients under 40 years of age with normal ovarian reserve with BMI<30, undergoing fresh embryo transfer with no history of poor ovarian response in previous cycles, with a normal endometrial thickness and with a normal male factor are included in the study.

Exclusion criteria

Patients of age>40 years, undergoing frozen embryo transfer, with poor ovarian reserve and those with PCOS, hyperprolactinemia and with uterine abnormalities that could affect implantation are excluded from the study.

All sub-fertile patients meeting the inclusion and exclusion criteria during the study period were subjected to controlled ovarian stimulation with antagonist protocol. The gonadotropin dose was individualised based on ovarian reserve tests (AMH and antral follicle count (AFC)) and previous response to ovarian stimulation. Patients were closely monitored through serial ultrasounds and hormonal blood tests. GnRh antagonist was added when one follicle has reached 14 mm size (flexible protocol followed).

Ovulation was triggered with either human chorionic gonadotropin or GnRH agonist once at least three follicles have reached a size of 18 mm. Serum progesterone levels were noted on the day of the trigger administration. Oocyte retrieval done 35 hours after the trigger injection and the number of metaphase II (MII) oocytes retrieved were documented. Embryo transfer was performed on day 3 following oocyte retrieval. All patients received luteal support in form of progesterone injections and oral progesterone, starting on the day of oocyte retrieval and continued until the pregnancy test.

Patients were instructed to perform a pregnancy test 16 days after embryo transfer. Those with a positive test were offered a transvaginal ultrasound 2 to 3 weeks later to confirm the viability and location of the pregnancy.

Hormonal assay

Baseline follicle stimulating hormone, luteinising hormone and anti mullerian hormone, estrogen were measured on day 2/3 of menses in the preceding cycle to ICSI cycle. Serum progesterone (P) was measured on the day of trigger administration. After oocyte retrieval, the number of mature oocytes (MII) were counted and serum P level /number of MII oocytes ratio was calculated.

Statistical analysis

All baseline patient characteristics including age, Body Mass Index (BMI), type and cause of subfertility, duration of subfertility and baseline ovarian reserve tests were collected. These data were entered into an Excel sheet for further statistical analysis. The ovarian response, embryological assessment and pregnancy outcomes were also recorded. Statistical analysis was conducted using SPSS software (Statistical Packages for Social Sciences) version 29.0.

Continuous variables were expressed as mean±standard error of the mean (SEM), while categorical data were presented as frequencies and percentages. To compare quantitative variables, an independent Student's t-test was used, while the Chi-square test was applied for categorical data. Receiver operating characteristic (ROC) curve analysis was employed to evaluate the overall performance of the different parameters in the study, allowing for a comparison of their diagnostic accuracy. A p value of<0.05 was considered statistically significant.

RESULTS

A total of 223 eligible patients were initially enrolled in the study. However, 12 patients were excluded from the final analysis due to the absence of embryo transfer. The reasons for exclusion were failed fertilization (n=1) or the decision to freeze all embryos due to a high risk of ovarian hyperstimulation syndrome (OHSS) (n=11). As a result, the final study population consisted of 211 patients.

The mean age of study population was 31.5±4.4 and the mean BMI of study population is 24.9±1.5 as shown in Table 1. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off for the P-trigger/MII oocyte ratio. The Area Under the Curve (AUC) was used to assess the predictive accuracy of this cut-off. Based on this analysis, a P-trigger/MII oocyte ratio cut-off of 0.29 was established. This cut-off was associated with a sensitivity of 94.1% and a specificity of 61.6% in predicting pregnancy outcomes in IVF/ICSI cycles, with an area under the curve (AUC) of 0.718 as shown below in Figure 1.

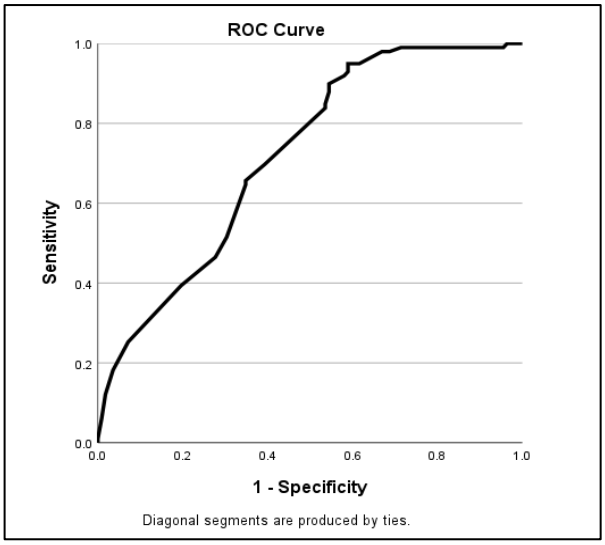

Figure 1: ROC curve determining the optimal cutoff for p- trigger / MII oocyte ratio.

Table 1: Demographic features and baseline hormones in the study population.

Parameter	Mean	Range	Minimum	Maximum
Age (in years)	31.5±4.4	19	23	40
BMI	24.9±1.5	8.1	21	29
Day 2 FSH	5.5±1.5	10.9	1.1	12
Day 2 LH	3.5±1.7	10.9	1.1	10
Day 2 E2 (pg/ml)	26.4±7.2	40.8	10.2	51
AMH (ng/ml)	2.1±0.77	3.6	0.9	4

Table 2: Comparison of baseline hormonal levels and gonadotropin dose and IVF outcomes between two groups.

Parameter	P/MII		P value
	≤0.29 (n=161) Mean±SD	>0.29 (n=50) Mean±SD	
Day 2 FSH	6.2±1.43	6.1±1.63	0.7
Day 2 LH	3.49±1.6	3.4±1.3	0.75
Day 2 E2	26.7±6.9	25.1±7.9	0.17
AMH	2.1±0.76	2.0±0.8	0.445
P4 on day of trigger	1.19±0.27	1.4±0.32	<0.01
Gonadotropin dose	2785±37	2830±28	0.7
Duration of stimulation	11.1±0.5	11.4±0.4	0.7
Total no. of oocytes	9.7±2.9	6.17±2.4	<0.01
MII oocytes	7.2±2.4	3.3±1.3	<0.01
fertilisation	7.1±2.6	3.3±1.4	<0.01
Embryos transferred	2.02±1	2.3±0.83	0.12
P/MII	0.17±0.04	0.52±0.38	<0.01

Table 3: Comparison of IVF outcomes between the two groups.

Parameter	P4/M2 (<0.29)	P4/M2 (>0.29)	P value
Clinical pregnancy	57.70%	20.40%	<0.01
Miscarriage rate	12.30%	4.20%	0.106
Live birth	25.20%	8.30%	0.012
Multiple pregnancy	36%	25%	0.2

While there were no statistically significant differences in baseline parameters, gonadotropin dose, duration of stimulation or the number of embryos transferred between the two groups, significant differences were observed in key IVF outcomes like the number of oocytes collected, No. of MII oocytes and fertilization rates ($p<0.01$). The P-trigger/MII oocyte ratio (≤0.29) group had significantly better outcomes in terms of total no. of oocytes collected, no. of MII oocytes collected and the fertilization rates when compared to P-trigger/MII oocyte ratio (>0.29) group as shown above in Table 2.

Using the cut off level of P/MII oocyte ratio of 0.29 as determined by the ROC curve, the clinical pregnancy rates and live birth rates (57.7% and 25.2% respectively) were significantly higher in patients with P/MII oocyte ratio≤0.29 as compared with patients with P/MII oocyte ratio>0.29 (20.4% and 8.3% respectively) with no significant difference in the miscarriage and multiple pregnancy rates between the two groups as shown above in Table 3.

DISCUSSION

This study explores the relationship between progesterone levels and oocyte quality in the context of assisted reproductive technology (ART), specifically focusing on predictors of implantation and clinical pregnancy in patients with normal ovarian reserve. The key finding of this study is that the progesterone-to-MII oocyte ratio (P/MII ratio) is a more accurate predictor of pregnancy outcomes. It has an area under the ROC curve (AUC) of 0.718, indicating strong predictive value.

This ratio is valuable because it reflects two critical factors that influence implantation, the progesterone levels acting as a marker for the hormonal environment, which is crucial for endometrial receptivity and the MII oocytes serving as a proxy for the quality of available embryos, which influences the potential for successful implantation. In our study we found that P4-trigger/MII oocyte ratio cut off of≤0.29 had significantly higher clinical pregnancy rates and live birth rates compared to those with a ratio of>0.29, however there is no significant difference in fertilization rates, miscarriage rates and multiple pregnancy rates between the two groups.

Ahmad et al, found that using a cutoff P-trigger/MII oocyte ratio of 0.125, patients with a ratio ≤0.125 had significantly higher implantation (29.2%) and clinical pregnancy rates (74.2%) compared to those with a ratio>0.125 (implantation rate of 11.3% and clinical pregnancy rate of 24.3%).[21] However, there was no significant difference in the fertilization rate between the two groups. Ibrahim Badr et al, demonstrated that the P-trigger/MII ratio of<0.18 showed a significantly higher clinical pregnancy rate compared to those with ratio of>0.18 following ICSI ($p<0.001$).[22]

Neeta Singh et al, found that the pregnancy rate was significantly higher (35.3%) in patients with a P-trigger/oocyte ratio≤0.15 compared to those with a ratio>0.15 (18.8%), with a p value of less than 0.001. However, there were no significant differences in fertilization and cleavage rates between the two groups ($p>0.05$).[23]

Li-Juan Huang et al, found that cut off for P-trigger/MII ratio of≤0.367 group had a significantly higher clinical pregnancy rate and live birth rate compared to P trigger/MII ratio of>0.367.[24] Li et al, in 2011 analysed endometrium by micro RNA and microarray techniques, suggested dissimilar endometrial changes in patients with high progesterone levels on the day of hCG administration and poor pregnancy rates.[25] A recent metanalysis and systematic review of over 60,000 IVF cycles by Venetis et al, showed that elevation of progesterone on day of hCG administration is associated with a significantly decreased clinical pregnancy rate in fresh IVF cycles using gonadotropins and GnRH analogues for ovarian stimulation.[14]

Abbas et al, suggested that increased progesterone causes advancement of endometrial maturation and impaired endometrial receptivity, they suggested that if Progesterone greater than 0.32 per metaphase 2 oocyte it's better to cancel embryo transfer and consider freezing all embryos for future transfer.[26]

Burns et al, in 114 IVF cycles, found that P/oocyte ratios were inversely associated with clinical pregnancy ($p<0.05$) and ongoing pregnancy ($p<0.02$).[27] Numerous studies have proposed varying threshold values of elevated progesterone (P) levels that may negatively affect the chances of pregnancy, ranging from 0.9 ng/ml to 3 ng/ml.[28] However, serum P levels by themselves may not be a good predictor of pregnancy success, as they may be influenced by several factors. The negative impact of elevated Progesterone levels on pregnancy outcomes can differ depending on the type of ovarian response. In an analysis of over 10,000 cycles by Xu et al, different threshold values for serum P levels based on ovarian response have been observed, these include 1.5 ng/ml for poor responders,1.75 ng/ml for intermediate responders and 2.25 ng/ml for high responders.[29] Therefore, the P-trigger/MII ratio may offer a more accurate prediction of pregnancy outcomes than serum P levels alone.

While this study is single centred and its retrospective design and inclusion of only patients with normal ovarian reserve limits its generalizability, future randomized trials are needed to further assess the P-trigger/MII oocyte ratio as a prognostic tool in IVF, potentially providing a more accurate prediction of outcomes.

CONCLUSION

The present study reveals that an elevated of P-trigger/MII oocyte ratio is inversely correlated with the probability of

pregnancy, indicating that this ratio may be a reliable predictor of IVF outcomes. Based on these findings, we suggest that the P/MII ratio could play a key role in selection of patients for cryopreservation of all embryos (elective freeze-all policy) and subsequent transfer of cryopreserved/thawed embryos. In clinical practice, each ART centre should establish its own cut-off for managing women with elevated Progesterone concentrations, taking into account potential variations in measurement techniques and accuracy, which could explain the differences in cut-off levels reported across various studies.

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